Peer Review File

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Reviewer A

An interesting case series discussing a timely topic.
Some changes are required in my opinion:

- a timeline summarizing the main events of this case report should be included. It would help the readability of the paper

Reply –
Time Lines for treatments were added in the case description. Please see page 6 and 7, lines 92 - 111
Times lines for calciphylaxis are also outlined in Figure 1. (Please see page 16)

- the discussion should be expanded and a more personal perspective should be included

Reply –
We appreciate this suggestion. In the discussion, we added risk factors for our patient. (Please see Page 10, lines 181-184.
Discussion about the pathophysiology of calciphylaxis is our perspective and brings strength to our paper. (Pages 10, 11, 12, please see lines 191 through 225)

We also added a brief paragraph about CCA and treatment options (Pages 8 and 9, lines 139 -152)

- The background of the role of systemic treatments in cholangiocarcinoma and predictive biomarkers to treatments should be better discussed, and some recent papers regarding this topic should be included (PMID: 33592561; PMID: 36633661; PMID: 33756174 ; PMID: 35031442), only for a matter of consistency

Reply-
We added a paragraph regarding CCA and treatments and all relevant references quoted and revised the discussion as suggested. (Pages 8 and 9, lines 139 -152)

- A linguistic revision is needed.

Reply - Linguistic revision was done throughout the paper.

Reviewer B

Chandana et al. documented a case of calciphylaxis as a rare adverse effect of FGFR inhibitor Pemigatinib in a patient with advanced cholangiocarcinoma of the liver. They also presented a concise summary of molecular mechanism underlying FGFR inhibitor-mediated calcinosis cutis. As such, this manuscript contains very educative contents and will merit publication. However, I dare say that English is not good enough though the authors seem to be Americans. Please check and revise English well.

1. (l.65) FGFR1-3 and received: FGFR1-3, received.

Reply 1: modified text as advised.
Changes in text: "FGFR1-3, received." (please see page 5 and line 75)

2. (l.83) steatohepatitis, diagnosed: steatohepatitis, was diagnosed.

   Reply 2: Modified text as advised.
   Changes in text: "steatohepatitis, was diagnosed." (Please see page 6 nd line 94)

3. (l.86) necessary disease in the lung: What does necessary disease mean?

   Reply 3: modified text as advised.
   Changes in text: "revealed disease in the lung"; the word "necessary" was removed.

4. (ll.86-87) chest lymph nodes: Please describe more accurately. Mediastinal lymph nodes or hilar or subcarinal lymph nodes?

   Reply 4: modified text as advised.
   Changes in text: " lung and mediastinum nodal metastasis" (Please see page 6, and line 105)

5. (l.93) As such patient: As such the patient.

   Reply 5: modified text as advised.
   Changes in text: "as such the patient"

6. (l.94) Patient was noted to have: The patient was noted….

   Reply 6: modified text as advised.
   Changes in text: "the patient was found to have."

7. (l.100) CRP of 22.9, PTH of 10.1, …: Please add units and normal range of the items.

   Reply 7: modified text as advised.
   Changes in text: "CRP of 22.9 mg/L (normal values <10mg/L), PTH of 10.1pg/ml (reference range 15-65 pg/ml)," (page 7, lines 120- 122)

8. (l.125) FGFRi-3 With: What does FHFRi-3 mean? Then, With should be with.

   Reply- FHFRi-3 is a type and deleted.

   Reply 8: modified text as advised.
9. (l.127) Palmar-plantar: palmar-plantar.

   Reply 9: modified text as advised.
   Changes in text: "palmar-plantar" (Please see page 9 , line 167)

10. (l.129) a case of pamigatatinib: a case of pemigatinib.

    Reply 10: modified text as advised.
    Changes in text: "a case of pemigatinib"

11. (l.158) production of MGP: Please explain MGP.

Reply 11: modified text as advised with added context
Changes to text: "FGF2 also induces production of Matrix Gla protein (MGP), a vitamin-K activated gene heavily involved in mineralization and a potent inhibitor of transdifferentiation and matrix vesicle release"; more evidence supporting the dysregulation of osteogenic and mineralization process leading to these deposits. (please see page 11, lines 202-203)

12. (l.191) This is the one of the only cases: This is the only case.

    Reply 12: modified text as advised.
    Changes to text: "This is the only case" (Please see page 13, line 237)

13. (l.193) and the current literature all while giving readers: and gives readers.

    Reply 13: modified text as advised.
    Changes to text: "and gives readers." (please see page 13, line 240)

14. Figure 3, CAPILLARY WALL MICROCALCIFICATIONS: The arrow does not appear to point to calcification. Please use thinner/smaller arrows/arrowheads to pinpoint calcification.

    Reply 14: modified image as advised; please see new thin blue arrows more accurately pointing to the calcifications in Figure 3.

Reviewer C

It is my great pleasure to have an opportunity to review this interesting case report. The authors presented a case of calciphylaxis in a patient treated with pemigatinib. In addition, it was successfully cared by efficient multidisciplinary treatments. This is a unique and interesting case report and will further our understanding of mechanism and treatment for calciphylaxis. I have some minor questions that I hope will help revise the manuscript.

1. Have you ever done von-Kossa staining? If done, please add the picture.

Reply – We have not done Von-Kossa staining

2. The treatment regimen should be added to the Figure 1.

   We added treatment regimens (treatment regimens for his cholangiocarcinoma) and treatment for calciphylaxis in the case description. It is difficult to add treatment regimens to Figure 1

Reviewer D

This case report describes a rare complication of fibroblast growth factor receptor (FGFR) inhibitor therapy. In light of the significant associated morbidity and mortality and the fact that diagnosis of calciphylaxis is often challenging and may require multiple biopsies even in the presence of clinical suspicion, it is important to be aware of this rare complication which may occur in settings outside of end stage renal disease. The authors include useful figures detailing the patient's timeline and laboratory values in addition to management strategies. Should the Editor extend an opportunity to revise the manuscript, there are multiple areas that require revision before further consideration for publication:

1. The use of the terminology calcinosis cutis and calciphylaxis could be clarified to ensure the readers do not get confused about the severity of the patient's presentation. Most dermatology and dermatopathology sources do not consider calciphylaxis to be a subtype of calcinosis cutis. While both are characterized by calcium deposition within the skin, calciphylaxis, specifically is defined by calcification within vasculature and has a significant associated morbidity.(Example reference text: Calonje E, Brenn T, Lazar A, McKee PH. McKee's pathology of the skin: with clinical correlations. 4 ed: Elsevier/Saunders; 2012.) It may be helpful to exclusively use the tercalciphylaxis rather than calcinosis cutis.

   Reply 1: modified text as advised
   Changes to text: to avoid confusion about pathology, the paper will use calciphylaxis exclusively while referring to the patient's condition. Changed throughout the paper

2. Abstract Line 33: These inhibitors target the fibroblast growth factor receptor rather than just fibroblast growth factor. This sentence should therefore read as "Small molecular fibroblast growth factor receptor (FGFR) inhibitors…"

   Reply 2: Modified text as advised.
   Changes to text: adjusted line 33 to "Small molecular fibroblast growth factor receptor (FGFR) inhibitors." (please see page 2 , line 33)

3. Abstract Line 48: The authors report "the patient we present did not have the renal and electrolyte abnormalities typically seen with this disease." However, in the body of the manuscript, the authors describe the patient as having hyperphosphatemia.

   Reply 3: modified text as advised to avoid confusion regarding electrolyte abnormalities. Removed any mention of normal phosphate.
   Changes to text: "did not have the high calcium levels and calcium dysregulation normally seen in the disease." (please see page 2, lines 49 -50)

4. Abstract, Line 49: The verbiage "more popular" is too colloquial for a scientific manuscript. Perhaps reword this sentence as: "As FGFR inhibitor use become more widespread…"

   Reply 4: modified text as advised.
   Changes to text: "As FGFR inhibitor use becomes more widespread." (please see page 2, line 51 and 52)

5. Generic drug names should be written in lower case.

   Reply 5: modified text as advised.
   Changes to text: "Pemigatinib" generic name changed to lower case.
   Please see throughout the paper

6. Key Findings: "Treatment plan" and "management" have very similar meanings; Only one of these needs to be included.

   Reply 6: Modified text as advised to avoid words of the same meaning.
   Changes to text: removed "management."

7. Key Findings: The word “lab work” is too colloquial.

   Reply 7: modified text as advised.
   Changes to text: changed “lab work” to “laboratory data.” (Please see page 4 in the last paragraph

8. Introduction, Line 65: The word “and” seems superfluous.

   Reply 8: modified text as advised; clearing up syntax in the sentence regarding approval use of pemigatinib
   Changes to text: ‘and was removed. Whole sentense deleted (Please see Page 5 , lines 71-73)

9. Did the patient have any other risk factors for calciphylaxis such as diabetes mellitus, obesity, autoimmune conditions, hypercoagulopathies or other associated medications (vitamin D, warfarin, iron, heparin injections)?

   Reply - To our knowledge, the patient has NASH-induced Cirrhosis and is also on Enoxaparin. These 2 factors may have a role in the development of calciphylaxis. We added these as risk factors in the discussion. (Please see page 10, liens 184- 185)

10. Some of the case description is less relevant to the calciphylaxis emphasis of the present report and could be summarized more concisely and/or removed. (Ex. “His AFP was normal. As such, biopsy of the liver lesion revealed adenocarcinoma, consistent with cholangiocarcinoma.”, discussion of thrombocytopenia, splenic embolization, and thrombosis. Trials of different chemotherapy regimens could be discussed more succinctly.)

    Reply 10: modified text as advised; the patient's coagulopathy history was more succinctly summarized and moved to lines 93-96. I feel this makes the case flow better.
    Changes to text: “This patient also has a history of thrombocytopenia secondary to his liver disease for which he underwent a partial splenic embolization. This was then complicated by a splenic vein thrombosis for which anticoagulation was started.” (Please see page 6, lines 93-96)

11. Many of the sentences in the Case Discussion use the noun “Patient” without a preceding article (like “the”). For example, in line 87, “Patient also has a history of thrombocytopenia secondary liver disease.” should have the word “the” before “patient”.

    Reply 11: Modified text as advised; definite articles (“the”) to define nouns are now correctly placed.
    Changes to text: “The patient” was used throughout the paper

12. Case Description Line 83: There seems to be a missing word between “steatohepatitis” and “diagnosed.” Perhaps “was”?

    Reply 12: modified text as advised
    Changes to text: “steatohepatitis, was diagnosed” (please see page 6, line 93)

13. Case Description Line 94: It would be informative to understanding potential risk factors the patient had to more thoroughly review the laboratory evaluation: What measures of renal function were assessed, and what specific lab values resulted? What was the patient’s phosphorous levels before initiating pemigatinib? It would also be useful to know the patient’s serum calcium and 25-hydroxyvitamin D levels and whether the patient had any laboratory evidence of coagulopathies.

Some of these values are nicely outlined in Figure 1, but would be useful to review in the body of the text as well.

Reply 13. We added the statement "Of note patient has normal kidney functions (Blood urea nitrogen, creatinine, glomerular filtration rate, calcium, and phosphorous level before starting pemigatinib". We already noted in the text that the patient was on anticoagulation with enoxaparin. Added a sentence about normal vitamin D levels. (Please see lines 119-124. Page 7)

14. All abbreviations should be defined (ex. AFP, WBC, PTH, ANCA, ANA, RF).

Reply 14: Modified text as advised

Changes to text: "Alpha fetal protein", "White blood cell", "Parathyroid hormone", "anti-neutrophil cytoplasmic antibodies", "anti-nuclear antibodies", "rheumatoid factor". ((Please see line 119-124. Page 7)

15. Case Description, Last paragraph: Was the Pemigatinib held as part of the initial calciphylaxis management? (Did the resolution occur three weeks after discontinuing Pemigatinib?) Did the patient's hyperparathyroidism and hyperphosphatemia resolve with the described management strategy as well?

Reply 15: Pemigatinib was discontinued afer the diagnosis of calciphylaxis. Patients hyperphospahtemnia resolved with appropriate management

modified text as advised: content clarification provided. Please see page 8, line 133-137)

16. Discussion section: It may be worth briefly reviewing risk factors for calciphylaxis in patients without end-stage kidney disease and describing which of these the patient had.

Reply 16: modified text as advised; text was added to inform risk factors including the patients risk factors for calciphylaxis
Changes to text: added lines 182-185 (Page 10) "Risk factors for developing calciphylaxis include female sex, end stage renal disease, warfarin use, systemic hypercoagulability, connective tissue diseases, repeated skin trauma from injections, diabetes, and liver disease to name the most prevalent. Among these, the patient had liver disease and was on low molecular weight heparin (enoxaparin)."

17. Figure 3: The term "subcutaneous" is more commonly used and understood than "hypodermic." Also the type of stain used should be listed in the figure caption.

Reply 17: modified text as advised; adjusted the figure caption
Changes to text: added "subcutaneous" and "H & E (hematoxylin-eosin) stain was used."

18. References: Reference number 4 only includes a hyperlink to a PDF.

Reply 18: modified text as advised; reference changed.
Changes to text: reference 4 "Bibeau, K., et al. (2022). "Progression-Free Survival in Patients With Cholangiocarcinoma With or Without FGF/FGFR Alterations: A FIGHT-202 Post Hoc Analysis of Prior Systemic Therapy Response." JCO Precis Oncol 6: e2100414.